Remarks

Courtesies extended to Applicants' representatives in the telephonic interview held on March 18, 2003, are acknowledged with appreciation.

As discussed during the interview, the present invention provides methods for modulating expression of exogenous genes in isolated cells containing a defined DNA construct (*i.e.*, claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55, and 57-71). DNA constructs contemplated herein comprise an exogenous gene under the control of a (modified or unmodified) response element plus a modified ecdysone receptor which, in the presence of an appropriate ligand, binds to the response element. Optionally, a second receptor member is included that acts as a silent partner for the modified ecdysone receptor. The invention method comprises providing to an isolated cell containing the construct an effective amount of a ligand(s) for the modified ecdysone receptor, wherein the ligand(s) is not normally present in the cell. The presence of ligand for the modified ecdysone receptor (and optionally, the presence of a silent partner) promotes the formation of ligand-receptor complexes that interact with corresponding response elements, thereby modulating expression of exogenous genes.

Invention methods are useful in a wide variety of applications. Modulation of exogenous gene expression is desirable in numerous isolated cell populations ranging from transiently modified cells to stably transformed cell lines. For example, invention methods can advantageously be employed in *in vitro* cellular expression systems to regulate expression of a recombinant expression product. Similarly, host cells and other recombinant cell types can benefit from invention methods for modulating the expression of an exogenous gene.

Claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55 and 57-77 were pending before this response. By this response, claims 1 and 22-24 have been amended to define Applicants' invention with greater particularity. These amendments add no new matter as they are fully supported by the specification and the original claims. In addition, claims 13 and 72-77 have been cancelled without prejudice. Applicants respectfully submit that the amendments presented herein place

the application in condition for allowance or, at a minimum, reduce the issues for appeal. Accordingly, entry of the amendments is respectfully requested.

Accordingly, claims 1, 3-9, 11, 12, 15-24, 39, 40, 47-55 and 57-71 are currently pending. The present status of all claims in the application is provided in the listing of claims presented herein beginning on page 2.

Initially, Applicants respectfully disagree with the Examiner's designation of the present Office Action as a Final Office Action on the grounds that the claims allegedly "could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114". To the contrary, the Examiner had denied entry of the same amendments after the prior final rejection because "they raise[d] new issues that would require further consideration and/or search" (see Advisory Action, Paper No, 41, mailed January 6, 2003). The Examiner's action is clearly improper because "it would not be proper to make final a first Office action in a continuing or substitute application [here an RCE] where that application contains material which was presented in the earlier application after final rejection [Applicants' amendments of 12/13/02; resubmitted with RCE] or closing of prosecution but was denied entry because (A) new issues were raised that required further consideration and/or search . . ." (MPEP § 706.07(b)). Accordingly, Applicants respectfully submit that the finality of this Office Action is premature, and request reconsideration and withdrawal of the finality of this Office Action.

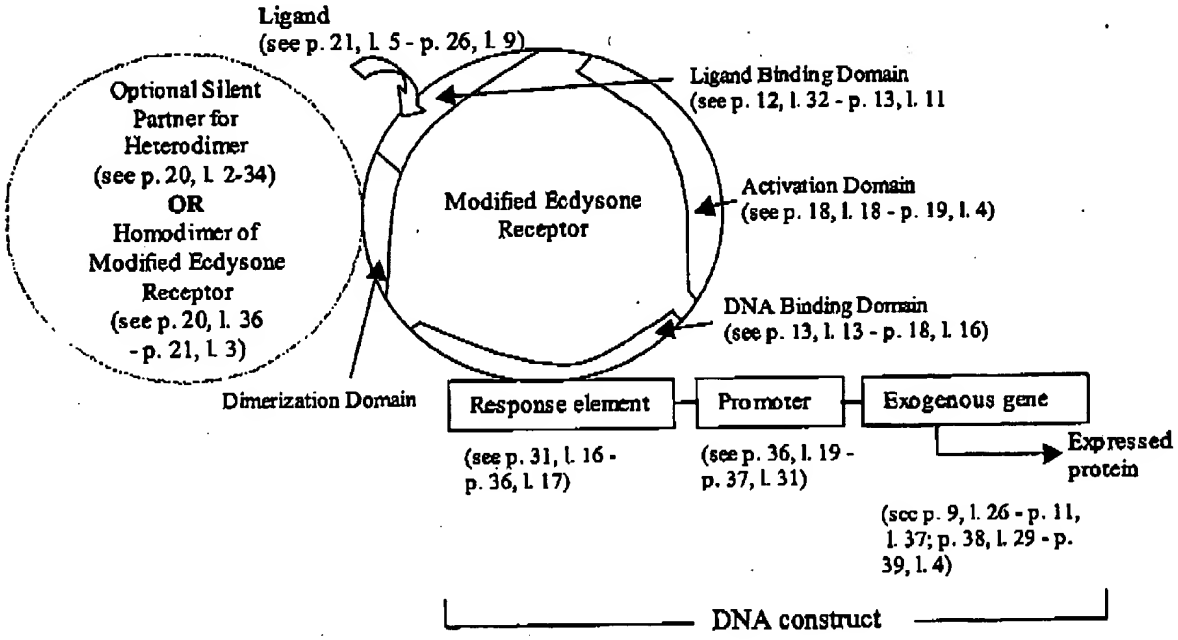
The rejection of claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55, 57-70 and 72-77 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention, is respectfully traversed.

Invention methods, as defined, for example, by claim 1, require providing to an isolated cell an effective amount of one or more ligands for a modified ecdysone receptor, wherein said

ligand(s) are not normally present in the cell. The cell contains a DNA construct composed of an exogenous gene under the control of a defined response element, *i.e.*, an element to which a modified ecdysone receptor binds; and a corresponding modified ecdysone receptor that binds to the response element in the presence of a ligand.

As discussed during the recent interview, Applicants respectfully submit that in view of the specification, one of skill in the art would have no reason to doubt that Applicants were in possession of the claimed methods for modulating gene expression. Applicants' method requires providing one or more ligands for a modified ecdysone receptor, which receptor binds to a response element that controls expression of a gene. Each component of the invention methods for modulating the expression of exogenous genes has been fully disclosed in the specification.

The following schematic illustrates all required components of the invention, and identifies substantial exemplary support in the specification for every required component.



Furthermore, exemplary support for each required component is clearly provided in the specification as indicated in the following Table.

Required component	Exemplary support in specification
Modified Ecdysone Receptor	
- ligand binding domain	page 12, line 32 through page 13, line 11
- activation domain	page 18, line 18 through page 19, line 4
- DNA binding domain	page 13, line 13 through page 18, line 16
DNA construct	
- response element	page 31, line 16 through page 36, line 17
- promoter	page 36, line 19 through page 37, line 31
- exogenous gene	page 9, line 26 through page 11, line 37 page 38, line 29 through page 39, line 4
Optional Silent Partner for Heterodimer	page 20, lines 2-34
or Homodimer of Modified Ecdysone Receptor	page 20, line 36 through page 21, line 3
Ligand	page 21, line 5 through page 26, line 9

Thus, each element of the pending claims is clearly depicted in detail in the specification as filed, with more than adequate relevant identifying characteristics including both structural and functional features of each element.

However, in efforts to advance prosecution and reduce the issues for appeal, independent claims 1 and 22-24 have been amended herein to further define the required response element. As amended the response element is a specific modified response element containing two clearly defined half-sites, which binds to the modified ecdysone receptor and does not bind to farnesoid X receptor (FXR). Independent claims 50 and 67-71 specifically require the response element to be an ecdysone response element.

In addition, claims 13 and 72-77 have been cancelled without prejudice herein. Accordingly, Applicants respectfully request reconsideration and withdrawal of the written description rejection of claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55, 57-70 and 72-77 under 35 U.S.C. § 112, first paragraph.

The rejection of claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55, 57-70 and 72-77 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide enablement for the method as claimed, is respectfully traversed. Applicants respectfully submit that the specification as filed enables any person skilled in the art to make and use the invention commensurate in scope with the present claims.

One of skill in the art could readily follow the specific teachings of the specification to modulate expression of an exogenous gene as claimed. Each element required by the present methods is fully described by the specification as filed, as noted above. Methods for creating DNA constructs encoding the contemplated receptor(s) and the exogenous gene(s) to be regulated, and for transfecting cells with these constructs, are standard routine molecular biological manipulations clearly known to one of skill in the art at the time of filing. Moreover, the specification provides additional guidance on the use of these standard procedures (see, *e.g.*, specification at page 38, line 29 through page 46, line 20). Moreover, all of the presently pending claims are directed to *in vitro* methods, *i.e.* performed in isolated cells. Accordingly, Applicants respectfully request reconsideration and withdrawal of the enablement rejection of claims 1, 3-9, 11-13, 15-24, 39, 40, 47-55, 57-70 and 72-77 under 35 U.S.C. § 112, first paragraph.

Conclusion

In view of the above amendments and remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: July 11, 2003

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